

L4 ANSWER 1 OF 1 MEDLINE
 ACCESSION NUMBER: 95316868 MEDLINE
 DOCUMENT NUMBER: 95316868 PubMed ID: 7796420
 TITLE: Topological control of p21WAF1/CIP1 expression in normal and neoplastic tissues.
 AUTHOR: el-Deiry W S; Tokino T; Waldman T; Oliner J D; Velculescu V
 CORPORATE SOURCE: E; Burrell M; Hill D E; Healy E; Rees J L; Hamilton S R; + Oncology Center, Johns Hopkins University School of Medicine, Baltimore, Maryland 21231, USA.
 CONTRACT NUMBER: CA43460 (NCI)
 CA62924 (NCI)
 GM07184 (NIGMS)
 SOURCE: CANCER RESEARCH, (1995 Jul 1) 55 (13) 2910-9.
 Journal code: 2984705R. ISSN: 0008-5472.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 OTHER SOURCE: GENBANK-U24170; GENBANK-U24171; GENBANK-U24172; GENBANK-U24173; GENBANK-U24174
 ENTRY MONTH: 199508
 ENTRY DATE: Entered STN: 19950817
 Last Updated on STN: 19950817
 Entered Medline: 19950801

AB The p53-regulated gene product p21WAF1/CIP1 is the prototype of a family of small proteins that negatively regulate the cell cycle. To learn more about p21WAF1/CIP1 regulation in vivo, monoclonal antibodies were developed for immunohistochemistry. These revealed that p21WAF1/CIP1 expression followed radiation-induced DNA damage in human skin in a pattern consistent with its regulation by p53. A detailed comparison of the human, rat, and mouse p21WAF1/CIP1 promoter sequences revealed that this induction was probably mediated by conserved p53-binding sites upstream of the transcription start site. In unirradiated tissues, p21WAF1/CIP1 expression was apparently independent of p53 and was observed in a variety of cell types. Moreover, there was a striking compartmentalization of p21WAF1/CIP1 expression throughout the gastrointestinal tract that correlated with proliferation rather than differentiation. As epithelial cells migrated up the crypts, the Ki67-expressing proliferating compartment near the crypt base ended abruptly, with the coincident appearance of a nonproliferating compartment expressing p21WAF1/CIP1. In colonic neoplasms, this distinct compartmentalization was largely abrogated. Cell cycle inhibitors are thus subject to precise topological control, and escape from this regulation may be a critical feature of neoplastic transformation.

L8 ANSWER 1 OF 2 MEDLINE DUPLICATE 1

ACCESSION NUMBER: 1999238075 MEDLINE

DOCUMENT NUMBER: 99238075 PubMed ID: 10223564

TITLE: Impact of the expression of cyclin-dependent kinase inhibitor p27Kip1 and **apoptosis** in tumor cells on the overall survival of patients with non-early stage gastric carcinoma.

AUTHOR: Ohtani M; Isozaki H; Fujii K; Nomura E; Niki M; Mabuchi H; Nishiguchi K; Toyoda M; Ishibashi T; Tanigawa N

CORPORATE SOURCE: Department of General and Gastroenterological Surgery, Osaka Medical College, Takatsuki City, Japan.

SOURCE: CANCER, (1999 Apr 15) 85 (8) 1711-8.
Journal code: 0374236. ISSN: 0008-543X.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals

ENTRY MONTH: 199905

ENTRY DATE: Entered STN: 19990525
Last Updated on STN: 19990525
Entered Medline: 19990513

AB BACKGROUND: The expression of p27Kip1 and **apoptosis** have been implicated in tumor aggressiveness and proved to be prognostic predictors for several human malignancies. In this study, the authors sought to investigate the expression of p27Kip1 and **apoptosis** and their potential significance in determining the prognosis of patients with non-early stage gastric carcinoma. METHODS: Primary gastric tumor specimens from 225 patients were investigated by **immunohistochemistry** with anti-p27Kip1 and anti-Ki-67 antibodies, and their **apoptotic** indices were determined with the use of an Apop-Tag in situ detection kit. RESULTS: The median p27Kip1 labeling index (LI) was 48.4%. There was a significant association between the p27 LIs and the **apoptotic** indices (AIs). However, there was no association between the p27 LIs and the Ki-67 LIs. p27 LI was demonstrated to be one of the most significant and independent prognostic factors in multivariate analysis. Although AI was found to be prognostically significant in univariate analysis, it failed to retain an independent and significant value regarding overall survival in multivariate analysis. CONCLUSIONS: Decreased expression of p27Kip1 and reduction of **apoptotic** potential were two of the most important factors in predicting a poor prognosis for patients with non-early stage gastric carcinoma. These findings support the hypothesis that decreased p27Kip1 expression, which may reflect a decreased rate of **apoptosis**, is closely related to the aggressiveness of gastric carcinoma. Therefore, the assessment of p27Kip1 expression and **apoptotic** potential may prove valuable in identifying patients with gastric carcinoma who are at high risk for recurrence and would benefit from adjuvant therapy.

L7 ANSWER 3 OF 3 MEDLINE DUPLICATE 1

ACCESSION NUMBER: 83061415 MEDLINE

DOCUMENT NUMBER: 83061415 PubMed ID: 6128497

TITLE: Case for adoptive immunotherapy in cancer.

AUTHOR: Berken A

SOURCE: LANCET, (1982 Nov 27) 2 (8309) 1190-2.
Journal code: 2985213R. ISSN: 0140-6736.

PUB. COUNTRY: ENGLAND: United Kingdom

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals

ENTRY MONTH: 198301

ENTRY DATE: Entered STN: 19900317
Last Updated on STN: 19950206
Entered Medline: 19830107

AB Patients with normal immune systems may be unable to mount effective defences against solid tumours because of (1) the generation of suppressor **T cells** in the low zone **tolerance** response elicited by the low concentrations of antigen furnished by **slow growing solid tumours**; (2) the ineffectiveness of the cytolytic **T-cell** response when the tumour cell membrane lacks the major histocompatibility gene products required for linkage to tumour antigens; and (3) the hindrance of antibody-dependent cellular cytotoxicity by antitumour antibodies when the precise requirements for the reaction cannot be fulfilled in the sites occupied by solid tumours. Recent immunological advances suggest that it should be possible to isolate antigens from cancer cells, produce antibodies against these antigens, bind the antibodies to the patient's macrophages and K lymphocytes, and reinject the bound cells into the patients to stimulate lymphokine synthesis and antibody-dependent cellular cytotoxicity.

L9 ANSWER 7 OF 11 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2000:149379 BIOSIS
DOCUMENT NUMBER: PREV200000149379
TITLE: Taxol and doxorubicin cytotoxicity: **Apoptotic**
signaling via different signals.
AUTHOR(S): **Bacus, SS (1)**; Gudkov, A.; Yarden, Y.
CORPORATE SOURCE: (1) Quantitative Diagnostics Laboratory, Elmhurst, IL,
60126 USA
SOURCE: Breast Cancer Research and Treatment., (1999) Vol. 57, No.
1, pp. 55.
Meeting Info.: 22nd Annual San Antonio Breast Cancer
Symposium San Antonio, Texas, USA December 8-11, 1999
ISSN: 0167-6806.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L9 ANSWER 9 OF 11 MEDLINE DUPLICATE 3
 ACCESSION NUMBER: 97280827 MEDLINE
 DOCUMENT NUMBER: 97280827 PubMed ID: 9135154
 TITLE: Transgenic mice with p53-responsive lacZ: p53 activity varies dramatically during normal development and determines radiation and drug sensitivity in vivo.
 AUTHOR: Komarova E A; Chernov M V; Franks R; Wang K; Armin G; Zelnick C R; Chin D M; **Bacus S S**; Stark G R; Gudkov A V
 CORPORATE SOURCE: Department of Genetics, University of Illinois at Chicago, 60607, USA.
 CONTRACT NUMBER: 3TW00475 (FIC)
 CA60730 (NCI)
 CA62045 (NCI)
 +
 SOURCE: EMBO JOURNAL, (1997 Mar 17) 16 (6) 1391-400.
 Journal code: 8208664. ISSN: 0261-4189.
 PUB. COUNTRY: ENGLAND: United Kingdom
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 199705
 ENTRY DATE: Entered STN: 19970602
 Last Updated on STN: 19970602
 Entered Medline: 19970520
 AB To analyze the involvement of p53-dependent transcriptional activation in normal development and in response to DNA damage in vivo, we created transgenic mice with a lacZ reporter gene under the control of a p53-responsive promoter. Five independent strains showed similar patterns of transgene expression. In untreated animals, lacZ expression was limited to the developing nervous system of embryos and newborn mice and was strongly decreased in the adult brain. gamma-irradiation or adriamycin treatment induced lacZ expression in the majority of cells of early embryos and in the spleen, thymus and small intestine in adult mice. Transgene expression was p53 dependent and coincided with the sites of strong p53 accumulation. The lacZ-expressing tissues and early embryos, unlike other adult tissues and late embryos, are characterized by high levels of p53 mRNA expression and respond to DNA damage by massive **apoptotic** cell death. Analysis of p53-null mice showed that this **apoptosis** is p53 dependent. These data suggest that p53 activity, monitored by the reporter lacZ transgene, is the determinant of radiation and drug sensitivity in vivo and indicate the importance of tissue and stage specificity of p53 regulation at the level of mRNA expression.

L10 ANSWER 9 OF 77

MEDLINE

DUPLICATE 4

ACCESSION NUMBER: 2000110810 MEDLINE
DOCUMENT NUMBER: 20110810 PubMed ID: 10646890
TITLE: Number of **apoptotic** cells as a prognostic
marker in invasive breast **cancer**.
AUTHOR: de Jong J S; van Diest P J; Baak J P
CORPORATE SOURCE: Department of Pathology, Free University Hospital
Amsterdam, The Netherlands.
SOURCE: BRITISH JOURNAL OF CANCER, (2000 Jan) 82 (2)
368-73.
Journal code: 0370635. ISSN: 0007-0920.
PUB. COUNTRY: SCOTLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200002
ENTRY DATE: Entered STN: 20000218
Last Updated on STN: 20000218
Entered Medline: 20000204

AB Apoptosis plays an important role in **tumorigenesis**.
Tumour growth is determined by the rate of cell proliferation and
cell death. We counted the number of apoptotic cells in haematoxylin and
eosin (H&E)-stained **tumour** sections in series of 172 grade I and
II invasive breast **cancers** with long-term follow-up. The number
of apoptotic cells in ten high-power fields were converted to the number
of apoptotic cells per mm² to obtain the apoptotic index (AI). The AI
showed a positive correlation to the mitotic activity index (MAI) (P =
0.0001), histological grade (P < 0.0001) and worse **tumour**
differentiation. Patients with high AI showed shorter overall survival
than patients with low AI in the total group as well as in the lymph
node-positive group. **Tumour** size, MAI, lymph node status and AI
were independent prognostic indicators in multivariate analysis. The AI
was shown to be of additional prognostic value to the MAI in the total
patients group as well as in the lymph node-positive group. The
correlation between the AI and the MAI points to linked mechanisms of
apoptosis and proliferation. Since apoptotic cells can be counted with
good reproducibility in H&E-stained **tumour** sections, the AI may
be used as an additional prognostic indicator in invasive breast
cancer.

L10 ANSWER 27 OF 77

MEDLINE

DUPLICATE 13

ACCESSION NUMBER: 2000034901 MEDLINE

DOCUMENT NUMBER: 20034901 PubMed ID: 10569613

TITLE: The utility of tissue transglutaminase as a **marker** of **apoptosis** during treatment and progression of prostate **cancer**.

AUTHOR: Rittmaster R S; Thomas L N; Wright A S; Murray S K; Carlson

CORPORATE SOURCE: K; Douglas R C; Yung J; Messieh M; Bell D; Lazier C B
Department of Medicine, Dalhousie University, Halifax, Nova

Scotia, Canada.

SOURCE: JOURNAL OF UROLOGY, (1999 Dec) 162 (6) 2165-9.
Journal code: 0376374. ISSN: 0022-5347.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals

ENTRY MONTH: 200001

ENTRY DATE: Entered STN: 20000114

Last Updated on STN: 20000114

Entered Medline: 20000106

AB PURPOSE: To determine the extent of cell proliferation and apoptosis during treatment and progression of prostate **cancer** and to determine whether staining for tissue transglutaminase is a better histological marker than TUNEL for neoadjuvant androgen ablation treatment

of localized prostate **cancer**. MATERIALS AND METHODS: Immunocytochemistry techniques were used on archival prostate tissue from four groups of men: 14 men with BPH, 18 men with untreated, localized prostate **cancer**, 21 men with localized prostate **cancer** who received neoadjuvant hormone therapy prior to prostatectomy and 18 men

with metastatic androgen-independent prostate **cancer**. Cell proliferation was evaluated by staining for the Ki67 nuclear antigen, and apoptosis was evaluated by staining for DNA fragmentation (TUNEL technique) and tissue transglutaminase (tTG). Image analysis was used to quantitate the results. RESULTS: TUNEL staining increased by 37% in localized prostate **cancer** compared with BPH, with a further increase of 43% seen after neoadjuvant therapy, although variation was such that neither was statistically significant. In androgen-independent **cancer**, TUNEL staining was decreased compared with neoadjuvant hormone treated **cancer** (p = 0.02). Staining for tTG was not increased in untreated prostate **cancer** compared with BPH; however, staining more than doubled after neoadjuvant therapy, compared with untreated prostate **cancer** (p = 0.04). Staining for tTG was markedly decreased in androgen-independent **cancer** (p = 0.07 compared with BPH and p = 0.0004 compared with neoadjuvant hormone treated

cancer). Ki67 immunoreactivity did not significantly change in localized prostate **cancer**, either before or after neoadjuvant therapy, compared with BPH, but it more than doubled in androgen-independent prostate **cancer** (p = 0.07 compared with BPH and p = 0.05 compared with untreated prostate **cancer**). CONCLUSIONS: This study shows that cell proliferation increases and apoptosis decreases as prostate **cancer** progresses to androgen independence, and, that of the markers used in this study, tissue transglutaminase most accurately reflects the anticipated effect of

neoadjuvant hormone therapy on localized prostate **cancer**. An
assessment of these parameters provides a valuable tool for appraising
new
prostate **cancer** therapies.

L10 ANSWER 28 OF 77 MEDLINE DUPLICATE 14

ACCESSION NUMBER: 2000159274 MEDLINE
DOCUMENT NUMBER: 20159274 PubMed ID: 10694951
TITLE: Prognostic significance of proliferative and
apoptotic markers in oral tongue squamous
cell carcinomas.
AUTHOR: Xie X; De Angelis P; Clausen O P; Boysen M
CORPORATE SOURCE: Department of Otolaryngology, National Hospital,
University of Oslo, Norway.
SOURCE: ORAL ONCOLOGY, (1999 Sep) 35 (5) 502-9.
Journal code: 9709118. ISSN: 1368-8375.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200003
ENTRY DATE: Entered STN: 20000327
Last Updated on STN: 20000327
Entered Medline: 20000316

AB The prognostic impact of proliferative and apoptotic markers was studied
in 85 T1-4 oral tongue squamous cell carcinomas (SCCs). Ki67
immunoreactivity and AgNOR counts, including mean AgNOR counts (mAgNOR)
and the percentage of nuclei with more than one AgNOR (pAgNOR > 1), were
used as proliferative parameters. The apoptotic index (AI) was assessed
using the TUNEL method. Bax expression was detected
immunohistochemically
and scored. Bax expression correlated positively with AI (p = 0.0122).
Ki67 correlated with both pAgNOR > 1 (p = 0.0042) and mAgNOR (p =
0.0189).
Low Bax expression and low AI correlated significantly with the
disease-free period (p = 0.0001 and p = 0.0024, respectively). High
values for Ki67, pAgNOR > 1 and mAgNOR correlated with poor prognosis (p
= 0.0021, p = 0.0001 and p = 0.0244, respectively). Combinations of
proliferative and apoptotic parameters were stronger predictors than
individual parameters (p < 0.0001). pAgNOR > 1-Bax expression appeared to
be the best combination (p < 0.0001). We conclude that proliferative and
apoptotic markers, especially their combinations, have prognostic value
in tongue SCC.

L10 ANSWER 39 OF 77 MEDLINE DUPLICATE 16
 ACCESSION NUMBER: 2000123659 MEDLINE
 DOCUMENT NUMBER: 20123659 PubMed ID: 10660263
 TITLE: Expression and hormonal regulation of rat ovarian interleukin-1beta converting enzyme, a putative **apoptotic marker**: endocrine- and paracrine-dependence.
 AUTHOR: Irahara M; Ando M; Kol S; Adashi E Y
 CORPORATE SOURCE: Department of Obstetrics and Gynecology, University of Maryland School of Medicine, Baltimore 21201, USA.
 CONTRACT NUMBER: HD-30288 (NICHD)
 SOURCE: JOURNAL OF REPRODUCTIVE IMMUNOLOGY, (1999 Nov) 45 (1) 67-79.
 Journal code: 8001906. ISSN: 0165-0378.
 PUB. COUNTRY: Ireland
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200003
 ENTRY DATE: Entered STN: 20000320
 Last Updated on STN: 20000320
 Entered Medline: 20000309

AB It is the purpose of this paper to assess the expression, cellular localization, and hormonal regulation of rat ovarian interleukin (IL)-1beta converting enzyme (ICE), a putative apoptotic marker. In agreement with previous observations ICE transcripts were noted in relatively increased abundance in the thymus, lung, spleen and small intestine. Although ICE transcripts were barely expressed in the untreated, immature rat ovary, they were apparent throughout a simulated estrous cycle. The in vivo expression of ovarian ICE rose gradually from 6 h after ovulation triggering to a peak (1.74-fold increase versus control, $P < 0.05$) 24 h after human chorionic gonadotropin administration, a marked and significant decrease to baseline being noted 24 h later. To examine the effect of in vitro culture on ovarian ICE gene expression, whole ovarian dispersates from immature rats were cultured without treatment for 72 h. ICE gene expression significantly ($P < 0.01$) increased to a maximum 24 h post plating (2.55-fold increase as compared with time zero). Treatment with IL-1beta was associated with a small but statistically insignificant increase in ovarian ICE gene expression. Similarly, provision of IL-1RA resulted in a modest, albeit statistically insignificant, decrease in ovarian ICE gene expression. Treatment with GnRH (but not FSH, LH or PMSG) significantly ($P < 0.05$) increased ovarian ICE gene expression (41.5% increase versus control). Treatment with dexamethasone (but not diethylstilbestrol, R5020 or R1881) produced a significant ($P < 0.05$) 42.3% decrease in ovarian ICE gene expression as compared with untreated controls. Treatment with TNF alpha (but not

ET-1, TGF alpha, TGF beta, IGF-I or bFGF) produced a significant ($P < 0.01$) 2.5-fold increase in ovarian ICE gene expression as compared with untreated controls. Taken together, our present findings: (1) reaffirm the ovarian expression of the ICE gene, (2) document a periovulatory increase in ovarian ICE gene expression, (3) show the inhibitory effect of glucocorticoids in this regard, and (4) establish TNF alpha as an upregulator. Taken together, these findings suggest a role for ovarian ICE either in the context of apoptosis/atresia or in the context of the

ovulatory process.

10 ANSWER 61 OF 77

MEDLINE

DUPLICATE 23

ACCESSION NUMBER: 96313760 MEDLINE
DOCUMENT NUMBER: 96313760 PubMed ID: 8694549
TITLE: **Apoptosis** and angiogenesis: two promising
tumor markers in breast **cancer**
(review).
AUTHOR: Wu J
CORPORATE SOURCE: Academic Department of Biochemistry, Royal Marsden
Hospital, London, U.K.
SOURCE: ANTICANCER RESEARCH, (1996 Jul-Aug) 16 (4B)
2233-9. Ref: 80
Journal code: 8102988. ISSN: 0250-7005.
PUB. COUNTRY: Greece
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199608
ENTRY DATE: Entered STN: 19960911
Last Updated on STN: 19960911
Entered Medline: 19960829

AB Mammary epithelial homeostasis is dependent not only on the rate of cell proliferation, but also on apoptosis, a genetically programmed process of autonomous cell death. Cell death in **tumours** is commonly attributed to the induction of apoptosis. Angiogenesis is the process leading to the formation of new blood vessels, and it has been proposed that **tumor** growth is angiogenesis dependent. This review focuses on the biological role of apoptosis and angiogenesis in the development and progression of breast **cancer**; on the multiple genetic pathways regulating apoptosis and angiogenesis in breast **cancer**; and on clinical data demonstrating the prognostic significance of apoptosis and angiogenesis in breast **cancer**. Although evidence has suggested that decreased apoptosis and increased angiogenesis may play important roles in the biological aggressiveness of breast **cancer**, their precise molecular mechanisms in mammary **tumorigenesis** are unknown. There is accumulating evidence that apoptotic pathways and angiogenic status are controlled by a number of regulators, including inducers and inhibitors relevant to the pathogenesis of breast **cancer**. The inhibition of angiogenesis limits **tumor** growth by elevating the incidence of apoptosis. Several clinical studies have shown that apoptosis and angiogenesis are novel prognostic indicators in breast **cancer**, and they may have predictive value for the response to anticancer treatments. A recent study suggested that increased apoptosis plays a role in the response to hormonal treatment of breast **cancer**. Other studies have indicated that patients with breast **cancer** with high angiogenic activity have a worse prognosis. Overall, the evidence suggests that the progressive inhibition of apoptosis and induction of angiogenesis may contribute to **tumor** initiation, growth and metastasis in the pathogenesis of breast **cancer**. Apoptosis and angiogenesis may be valuable as markers for response in patients having primary or adjuvant chemotherapy for breast **cancer**. Furthermore, such **tumor** markers have the potential to develop a promising therapeutic strategy to regulate cell survival/death and neovascularization in breast **cancer** by the induction of apoptosis and/or the inhibition of

angiogenesis.

L10 ANSWER 63 OF 77

MEDLINE

DUPLICATE 24

ACCESSION NUMBER: 96400067 MEDLINE

DOCUMENT NUMBER: 96400067 PubMed ID: 8806443

TITLE: Monoclonal antibody to single-stranded DNA is a specific and sensitive cellular **marker** of **apoptosis**.

AUTHOR: Frankfurt O S; Robb J A; Sugarbaker E V; Villa L

CORPORATE SOURCE: Department of Pathology, Cedars Medical Center, Miami, Florida 33136, USA.

CONTRACT NUMBER: CA-50677 (NCI)

SOURCE: EXPERIMENTAL CELL RESEARCH, (1996 Aug 1) 226 (2) 387-97.

Journal code: 0373226. ISSN: 0014-4827.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199610

ENTRY DATE: Entered STN: 19961106

Last Updated on STN: 19970203

Entered Medline: 19961024

AB The most widely used histochemical marker of apoptosis (in situ end labeling, TUNEL) detects both apoptotic and necrotic cells and evaluates only late stages of apoptosis. Hence, a specific and sensitive cellular marker of apoptosis is needed to determine the role of apoptotic death in biology and pathology. The present study describes a novel immunohistochemical procedure for the staining of apoptotic cells using a monoclonal antibody (MAb) to single-stranded DNA. This MAb stained all cells with the morphology typical of apoptosis in etoposide-treated

HL-60,

MOLT-4, and R9 cell cultures, in which apoptosis was accompanied by high, moderate, and low levels of internucleosomal DNA fragmentation, respectively. TUNEL stained all apoptotic cells in HL-60 cultures, nearly

60% of apoptotic cells in MOLT-4 cultures, and only 14% of apoptotic cells

in R9 cultures. Apoptotic R9 cells, which progressed into secondary necrosis, retained MAb staining and became TUNEL-positive. Necrotic cells

in MOLT-4 cultures treated with sodium azide were stained by TUNEL, but were negative for MAb staining. All floating cells at a late stage of apoptosis in MDA-MB-468 cultures treated with cisplatin were stained by both MAb and TUNEL. However, among adherent cells in the early stages of apoptosis, MAb stained nearly 20 times more cells than TUNEL. In histological sections of human **tumor** xenografts, MAb detected clusters of apoptotic cells in viable **tumor** tissue, but did not stain cells in areas of central ischemic necrosis. In contrast, TUNEL stained nuclei in necrotic areas. Thus, MAb to single-stranded DNA is a specific and sensitive cellular marker of apoptosis, which differentiates between apoptosis and necrosis and detects cells in the early stages of apoptosis.

L10 ANSWER 64 OF 77 MEDLINE

DUPLICATE 25

ACCESSION NUMBER: 97060385 MEDLINE
DOCUMENT NUMBER: 97060385 PubMed ID: 8903420
TITLE: 1,25-Dihydroxyvitamin D3 induces morphological and
biochemical **markers** of **apoptosis** in
MCF-7 breast **cancer** cells.
AUTHOR: Simboli-Campbell M; Narvaez C J; Tenniswood M; Welsh J
CORPORATE SOURCE: Department of Biochemistry, University of Ottawa, Canada.
SOURCE: JOURNAL OF STEROID BIOCHEMISTRY AND MOLECULAR BIOLOGY,
(1996 Jul) 58 (4) 367-76.
Journal code: 9015483. ISSN: 0960-0760.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199612
ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 19980206
Entered Medline: 19961218

AB 1,25-Dihydroxyvitamin D3 [1,25(OH)2(D)3], the active metabolite of
vitamin

D, is a potent inhibitor of breast **cancer** cell growth both in
vivo and in vitro. To complement data which documents the
anti-proliferative effects of 1,25(OH)2(D)3, we assessed the role of
apoptosis in vitamin D-mediated growth arrest of MCF-7 cells. Time
course

studies indicated that 100 nM 1,25(OH)2(D)3 significantly reduces MCF-7
cell numbers within 48 h of treatment. Morphological assessment
demonstrated that MCF-7 cells treated with 1,25(OH)2(D)3 for 48 h exhibit
characteristic apoptotic features, including cytoplasmic condensation,
pyknotic nuclei, condensed chromatin and nuclear matrix re-organization.
In situ end labelling with terminal transferase indicated that cells
exhibiting apoptotic morphology in 1,25(OH)2(D)3-treated cultures were
positive for DNA strand breaks. These morphological features of

apoptosis
were accompanied by an increase in the cell death rate assessed as
soluble

DNA-histone complexes indicative of DNA fragmentation. To complement the
morphological data, we assessed the temporal expression of two proteins
which have been associated with apoptosis in mammary cells and
tumors. The steady state mRNA levels for TRPM-2/clusterin and
cathepsin B mRNA were significantly up-regulated in MCF-7 cells treated
with 1,25(OH)2(D)3 compared to control cells. Time-dependent increases

in
the expression of TRPM-2/clusterin and cathepsin B proteins were detected
by Western blotting in 1,25(OH)2(D)3-treated cells. These findings
indicate that, in addition to its anti-proliferative effects,
1,25(OH)2(D)3 activates the apoptotic cell death pathway in MCF-7 breast
cancer cells.

ACCESSION NUMBER: 95034044 MEDLINE
DOCUMENT NUMBER: 95034044 PubMed ID: 7947088
TITLE: Cleaved intracellular plasminogen activator inhibitor 2 in human myeloleukaemia cells is a **marker** of **apoptosis**.
AUTHOR: Jensen P H; Cressey L I; Gjertsen B T; Madsen P; Mellgren G; Hokland P; Gliemann J; Doskeland S O; Lanotte M; Vintermyr O K
CORPORATE SOURCE: Department of Medical Biochemistry, Aarhus University, Denmark.
SOURCE: BRITISH JOURNAL OF CANCER, (1994 Nov) 70 (5) 834-40.
Journal code: 0370635. ISSN: 0007-0920.
PUB. COUNTRY: SCOTLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199412
ENTRY DATE: Entered STN: 19950110
Last Updated on STN: 19980206
Entered Medline: 19941222

AB The proteolytic modification of plasminogen activator inhibitor 2 (PAI-2) was studied during apoptosis in the human promyelocytic **leukaemic** NB4 cell line during treatment with the phosphatase inhibitors okadaic acid and calyculin A as well as the protein synthesis inhibitor cycloheximide. The apoptic type of cell death was ascertained by morphological and biochemical criteria. In cell homogenates PAI-2 was probed by [¹²⁵I]urokinase plasminogen activator (uPA) and detected as a sodium dodecyl sulphate-stable M(r) 80,000 complex after reducing sodium dodecyl sulphate-polyacrylamide gel electrophoresis and autoradiography. During apoptosis a smaller (M(r) 70,000) uPA-PAI-2 complex was consistently detected. The modification was in the PAI-2 moiety, as the [¹²⁵I]uPA tracer could be extracted in its intact form from the complex. Thus the cleaved PAI-2 isoform is a biochemical marker of apoptosis in the promyelocytic NB4 cell line. The modified PAI-2 isoform was also detected in homogenates made from purified human mononuclear **leukaemic** cells aspirated from the bone marrow of patients suffering from acute and chronic myeloid **leukaemia**.

L10 ANSWER 75 OF 77

MEDLINE

DUPLICATE 28

ACCESSION NUMBER: 94249434 MEDLINE

DOCUMENT NUMBER: 94249434 PubMed ID: 8191917

TITLE: Synergistic effect of **tumor** necrosis factor-alpha
and interferon-alpha on the induction of apoptosis

detected

by BM-1/JIMRO: a new **marker** of **apoptosis**

AUTHOR: Zhang W; Naomoto Y; Tanaka N; Hizuta A; Orita K

CORPORATE SOURCE: First Department of Surgery, Okayama University Medical
School, Japan.

SOURCE: ACTA MEDICA OKAYAMA, (1994 Feb) 48 (1) 51-5.

Journal code: 0417611. ISSN: 0386-300X.

PUB. COUNTRY: Japan

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199406

ENTRY DATE: Entered STN: 19940629

Last Updated on STN: 19970203

Entered Medline: 19940623

AB The effects of the combination of natural human **tumor** necrosis factor-alpha (nHuTNF-alpha) and natural human interferon-alpha (nHuIFN-alpha) on the induction of apoptosis were investigated by immunohistochemical analysis with BM-1/JIMRO monoclonal antibody in RPMI 4788 **tumor** cells. Few **tumor** cells in the control culture could spontaneously undergo apoptosis. The number of positive cells increased at 2 and 4 h after treatment with nHuTNF-alpha (1 x 10(5) U/ml) and nHuIFN-alpha (1 x 10(5) IU/ml). This effect was clearly maintained from 8 h up to 72 h of culture. The number of apoptotic cells also greatly increased with doses, suggesting that the apoptosis induced by nHuTNF-alpha and nHuIFN-alpha in combination was dose-dependent. nHuTNF-alpha or nHuIFN-alpha alone could induce apoptosis, but the induction increased significantly when the two cytokines were combined. These findings indicate that by combining nHuTNF-alpha and nHuIFN-alpha apoptosis can be synergistically induced in RPMI 4788 **tumor** cells, and may have specific therapeutic implications for clinical treatments using these two cytokines.

L10 ANSWER 76 OF 77 MEDLINE DUPLICATE 29

ACCESSION NUMBER: 93364894 MEDLINE

DOCUMENT NUMBER: 93364894 PubMed ID: 8358726

TITLE: Specific proteolytic cleavage of poly(ADP-ribose) polymerase: an early **marker** of chemotherapy-induced **apoptosis**.

AUTHOR: Kaufmann S H; Desnoyers S; Ottaviano Y; Davidson N E; Poirier G G

CORPORATE SOURCE: Oncology Center, Johns Hopkins Hospital, Baltimore, Maryland 21287.

CONTRACT NUMBER: CA50435 (NCI)

CA55642 (NCI)

CA57545 (NCI)

SOURCE: CANCER RESEARCH, (1993 Sep 1) 53 (17) 3976-85.
Journal code: 2984705R. ISSN: 0008-5472.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199309

ENTRY DATE: Entered STN: 19931015
Last Updated on STN: 19931015
Entered Medline: 19930924

AB Apoptosis is a morphologically and biochemically distinct form of cell death that occurs under a variety of physiological and pathological conditions. In the present study, the proteolytic cleavage of poly(ADP-ribose) polymerase (pADPRp) during the course of chemotherapy-induced apoptosis was examined. Treatment of HL-60 human **leukemia** cells with the topoisomerase II-directed anticancer agent etoposide resulted in morphological changes characteristic of apoptosis. Endonucleolytic degradation of DNA to generate nucleosomal fragments occurred simultaneously. Western blotting with epitope-specific monoclonal and polyclonal antibodies revealed that these characteristic apoptotic changes were accompanied by early, quantitative cleavage of the M(r) 116,000 pADPRp polypeptide to an M(r) approximately 25,000 fragment containing the amino-terminal DNA-binding domain of pADPRp and an M(r) approximately 85,000 fragment containing the automodification and catalytic domains. Activity blotting revealed that the M(r) approximately 85,000 fragment retained basal pADPRp activity but was not activated by exogenous nicked DNA. Similar cleavage of pADPRp was observed after exposure of HL-60 cells to a variety of chemotherapeutic agents including cis-diaminedichloroplatinum(II), colcemid, 1-beta-D-arabinofuranosylcytosine, and methotrexate; to gamma-irradiation; or to the protein synthesis inhibitors puromycin or cycloheximide. Similar changes were observed in MDA-MB-468 human breast **cancer** cells treated with trifluorothymidine or 5-fluoro-2'-deoxyuridine and in gamma-irradiated or glucocorticoid-treated rat thymocytes undergoing apoptosis. Treatment with several compounds (tosyl-L-lysine chloromethyl ketone, tosyl-L-phenylalanine chloromethyl ketone, N-ethylmaleimide, iodoacetamide) prevented both the proteolytic cleavage of pADPRp and the internucleosomal fragmentation of DNA. The results suggest that proteolytic cleavage of pADPRp, in addition to being an early marker of chemotherapy-induced apoptosis, might reflect more widespread proteolysis that is a critical biochemical event early during the process of physiological cell death.

L12 ANSWER 33 OF 38 MEDLINE

ACCESSION NUMBER: 92277689 MEDLINE
DOCUMENT NUMBER: 92277689 PubMed ID: 1317462
TITLE: Accumulation of p53 tumor suppressor gene protein: an independent marker of prognosis in breast cancers.
AUTHOR: Thor A D; Moore DH I I; Edgerton S M; Kawasaki E S; Reihnsaus E; Lynch H T; Marcus J N; Schwartz L; Chen L C; Mayall B H; +
CORPORATE SOURCE: Department of Pathology, Massachusetts General Hospital, Boston 02114.
CONTRACT NUMBER: CA-44768 (NCI)
CA-48802 (NCI)
SOURCE: JOURNAL OF THE NATIONAL CANCER INSTITUTE, (1992 Jun 3) 84 (11) 845-55.
Journal code: 7503089. ISSN: 0027-8874.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199206
ENTRY DATE: Entered STN: 19920710
Last Updated on STN: 19920710
Entered Medline: 19920626

AB BACKGROUND: Mutations of the tumor suppressor gene p53 have been identified in breast cancer cell lines, and some breast carcinomas are detectable by **immunohistochemical** assay because of p53 protein accumulation. PURPOSE: This study was designed to determine whether p53 protein accumulation in breast cancers correlates with p53 gene mutation, with survival, and with five pathobiologic factors associated with prognosis. METHODS: IgG1 monoclonal **antibody** to **human p53** protein (PAb 1801) and **immunohistochemical** methods were used to detect p53 protein accumulation in archival formalin-fixed, paraffin-embedded, randomly selected carcinomas. We studied 295 invasive ductal carcinomas from the Massachusetts General Hospital; 151 were determined to be sporadic (not hereditary). We also studied 97 invasive ductal carcinomas--21 sporadic and 76 familial (hereditary)--from Creighton University. In addition, we examined 31 archival in situ carcinomas, 15 snap-frozen invasive ductal carcinomas, primary cell cultures from three benign breast tissue samples, and breast carcinoma cell lines MDA-MB-231 and MDA-MB-468. RESULTS: Nuclear p53 protein was observed in 16% of the 31 in situ carcinomas, 22% of the 172 sporadic carcinomas, 34% of the 50 tumors from patients with familial breast cancer, 52% of the 23 tumors from patients with the familial breast and ovarian cancer syndrome, and all three tumors from two patients with the Li-Fraumeni syndrome. There was complete concordance between p53 gene mutation and p53 protein accumulation in the 15 snap-frozen carcinomas and in both breast carcinoma cell lines. Statistically significant associations of p53 protein accumulation with estrogen receptor negativity and with high nuclear grade were found. There were statistically significant associations, independent of other prognostic factors, between p53 protein accumulation and metastasis-free and overall survival, for randomly accrued and for both sporadic and familial tumors. CONCLUSIONS: **Immunohistochemically** detected p53 protein accumulation was an independent marker of shortened survival and was seen more often in

familial than in sporadic carcinomas. Our findings also suggest a correlation between p53 protein accumulation and p53 gene mutation.

L12 ANSWER 37 OF 38 MEDLINE

ACCESSION NUMBER: 92036828 MEDLINE

DOCUMENT NUMBER: 92036828 PubMed ID: 1935458

TITLE: Flow cytometric measurement of p53 protein expression and DNA content in paraffin-embedded tissue from bronchial carcinomas.

AUTHOR: Morkve O; Laerum O D

CORPORATE SOURCE: Gade Institute, Department of Pathology, Haukeland Hospital, University of Bergen, Norway.

SOURCE: CYTOMETRY, (1991) 12 (5) 438-44.
Journal code: 8102328. ISSN: 0196-4763.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199112

ENTRY DATE: Entered STN: 19920124

Last Updated on STN: 19920124

Entered Medline: 19911212

AB The nuclear protein p53 has been measured in archival lung cancer biopsies. The monoclonal **antibody** PAb 1801, which recognizes **human p53**, was used. After immunostaining, the nuclei prepared from paraffin-embedded tissue were stained with propidium iodide for simultaneous measurement of DNA content; 17 of 24 lung cancers were p53 positive. The S-phase fraction in positive tumors was 22.9 +/- 6.4%, as compared to 13.6 +/- 6.1% in negative tumors (P less than 0.02). In ten of the positive tumors (two small cell carcinomas and eight non-small cell carcinomas), the p53 expression varied through cell cycle, whereas

in

seven tumors (five small cell carcinomas and two non-small cell carcinomas), no such variation of p53 expression was observed. Freezing the nuclear suspensions did not substantially reduce the p53 signals. Control experiments with the SV40-transformed human foreskin fibroblast cell line HSF4-T12 showed that the enzymatic digestion utilized to dissociate paraffin-embedded tissue did not significantly reduce p53 fluorescence. **Immunohistochemical** staining of biopsy specimens indicated that only cancer cells were overexpressing p53. In conclusion, using the monoclonal antibody PAb 1801, p53 is detectable in cell nuclei prepared from paraffin-embedded bronchial carcinoma biopsies. P53 positive tumors have increased proliferative activity compared to p53 negative tumors. Furthermore, the lack of cell cycle variation of p53 in small cell carcinomas indicates that this pattern may be related to high-grade malignancy.

L14 ANSWER 8 OF 8 MEDLINE
 ACCESSION NUMBER: 92235128 MEDLINE
 DOCUMENT NUMBER: 92235128 PubMed ID: 1569122
 TITLE: Analysis of p53 expression in human tumours: an
antibody raised against **human p53**
 expressed in Escherichia coli.
 AUTHOR: Midgley C A; Fisher C J; Bartek J; Vojtesek B; Lane D;
 Barnes D M
 CORPORATE SOURCE: Department of Biochemistry, University of Dundee, UK.
 SOURCE: JOURNAL OF CELL SCIENCE, (1992 Jan) 101 (Pt 1)
 183-9.
 Journal code: 0052457. ISSN: 0021-9533.
 PUB. COUNTRY: ENGLAND: United Kingdom
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 199205
 ENTRY DATE: Entered STN: 19920612
 Last Updated on STN: 19970203
 Entered Medline: 19920526

AB A cDNA encoding the complete normal human p53 protein was expressed in Escherichia coli using an expression system based on the bacteriophage T7 promoter. The cDNA was adapted so that the full-length protein was produced without fusion to any other sequence. Large amounts of the protein were isolated and the purified protein used to produce very high titre polyclonal antibodies to p53. These new antibodies permit the sensitive detection of p53 and p53 complexes in ELISA and immunoblotting assays. Most importantly, they also permit the detection of p53 in archival tumour material that has been conventionally fixed in formalin and embedded in paraffin wax. Using this reagent we have found that aberrant expression of p53 is a frequent feature of human **breast** cancer. We are able to recognise six different classes of p53 expression pattern that may be of help in the subclassification of **breast** tumours.

L15 ANSWER 17 OF 17 MEDLINE DUPLICATE 11
 ACCESSION NUMBER: 1998050227 MEDLINE
 DOCUMENT NUMBER: 98050227 PubMed ID: 9388844
 TITLE: Expression of CDKN2 gene product in human bronchogenic carcinoma.
 AUTHOR: Jiang Y; Xia S; Dai X
 CORPORATE SOURCE: Cancer Research Institute, China Medical University, Shenyang.
 SOURCE: CHUNG-HUA CHIEH HO HO HU HSI TSA CHIH CHINESE JOURNAL OF TUBERCULOSIS AND RESPIRATORY DISEASES, (1996 Apr) 19 (2) 81-3.
 Journal code: 8712226. ISSN: 1001-0939.
 PUB. COUNTRY: China
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: Chinese
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 199712
 ENTRY DATE: Entered STN: 19980109
 Last Updated on STN: 19980109
 Entered Medline: 19971223
 AB OBJECTIVE: To examine the expression of P16 protein in bronchogenic carcinoma and normal tissue adjacent to carcinoma and to determine the relationship between the gene and bronchogenic carcinoma. METHOD: Using
 a rabbit polyclonal **antibody** against **P16** (N-20), the expression of P16 protein was studied **immunohistochemically** on formalin fixed, paraffin embedded sections. RESULTS: The cytoplasmic P16 protein was mainly present in normal bronchial epithelium (93.8%), serous gland (92.6%) and alveolar epithelium (71.4%), the expression levels of P16 were significantly lower in carcinoma tissues (61.9%) when compared
 to levels in their normal counterparts ($P < 0.01$). Among tumors, squamous cell carcinomas and small cell carcinomas exhibited lower P16 expression levels compared with adenocarcinomas ($P < 0.01$). The expression levels
 of P16 were lower in poorly-differentiated adenocarcinomas compared with those in well-differentiated adenocarcinomas ($P < 0.05$). CONCLUSIONS:
 The results suggested that CDKN2 gene was a tumor suppressor gene, the inactivation of which were involved in the carcinogenesis of bronchogenic carcinoma and implicated in tumor differentiation.

L18 ANSWER 1 OF 1 MEDLINE DUPLICATE 1
 ACCESSION NUMBER: 1999077396 MEDLINE
 DOCUMENT NUMBER: 99077396 PubMed ID: 9862580
 TITLE: Aberrant cytoplasmic expression of the p16 protein in
breast cancer is associated with accelerated tumour
 proliferation.
 AUTHOR: Emig R; Magener A; Ehemann V; Meyer A; Stilgenbauer F;
 Volkmann M; Wallwiener D; Sinn H P
 CORPORATE SOURCE: Frauenklinik, Tübingen, Germany.
 SOURCE: BRITISH JOURNAL OF CANCER, (1998 Dec) 78(12)
 1661-8.
 Journal code: 0370635. ISSN: 0007-0920.
 PUB. COUNTRY: SCOTLAND: United Kingdom
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 199901
 ENTRY DATE: Entered STN: 19990128
 Last Updated on STN: 19990128
 Entered Medline: 19990108

AB The p16 protein plays an important role in the transition of cells into
 the G1 phase of the cell cycle. We have studied the prevalence of p16
 protein expression in **breast** carcinomas in a prospective series
 of 368 invasive and 52 non-invasive malignancies, as well as in 88
 locally
 recurring tumours and three tumour cell lines. p16 protein expression was
 evaluated **immunohistochemically** on paraffin sections using
 monoclonal and polyclonal **anti-p16 antibodies**
 , and by immunoblotting of tumour cell suspensions. Tumour cell lines
 were also subjected to polymerase chain reaction-single strand
 polymorphism (PCR-SSCP) analysis and direct DNA sequencing. The results
 were compared with established prognostic parameters, DNA flow cytometry
 and p53 protein expression. In 33 (9%) invasive and two (4%) intraductal
 carcinomas, a cytoplasmic accumulation of the p16 protein was seen.
 These
 cases were characterized by poor histological grade of differentiation,
 loss of oestrogen receptors and progesterone receptors and frequent
 overexpression of the p53 protein. In addition, **breast**
 carcinomas with aberrant p16 expression demonstrated a high proliferative
 activity, with median S-phase fractions 74% higher than in the control
 group and the median Ki67 fractions elevated to 75%. A genetic
 alteration
 of the p16 gene was not detectable in three analysed cell lines with
 cytoplasmic p16 expression applying PCR-SSCP and direct DNA sequencing.
 These results indicate that cytoplasmic accumulation of the p16 protein
 identifies a subset of highly malignant **breast** carcinomas with
 accelerated tumour proliferation and other unfavourable parameters in
breast cancer. The described protein accumulation is apparently
 not caused by an alteration of the p16 gene.

L18 ANSWER 32 OF 59 MEDLINE

ACCESSION NUMBER: 97065016 MEDLINE

DOCUMENT NUMBER: 97065016 PubMed ID: 8908566

TITLE: Apoptosis in chronic gastritis: evaluation of the gastric mucosa by DNA flow cytometry and the expression of the high

molecular weight cytokeratin.

AUTHOR: Attallah A M; Abdel-Wahab M; Elshal M F; Zalata K R; Ibrahim N M; Ezzat F

CORPORATE SOURCE: Biotechnology Research Laboratories, Mansoura University, Egypt.

SOURCE: HEPATO-GASTROENTEROLOGY, (1996 Sep-Oct) 43 (11) 1305-12.

Journal code: 8007849. ISSN: 0172-6390.

PUB. COUNTRY: Greece

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199702

ENTRY DATE: Entered STN: 19970227

Last Updated on STN: 19970227

Entered Medline: 19970213

AB BACKGROUND/AIMS: A series of premalignant lesions, including chronic gastritis (CG), intestinal metaplasia (IM) and dysplasia are associated with gastric carcinogenesis. The present study aimed to define these precancerous gastric lesions further by the study of the cellular DNA using flow cytometry, and the expression of the high molecular weight (68 KDa) Cytokeratin "CK1" proposed as a **marker** for epithelial cells dying by **apoptosis**. MATERIAL AND METHODS: Multiple antral biopsies from each of 92 cases with gastric dyspepsia were subjected for DNA content analysis using flow cytometry, and immunostaining using anti-CK1 monoclonal **antibody**. RESULTS: Chronic gastritis (CG) was present in 85 (92.4%) of cases, 14/85 (16.5%) cases showed chronic superficial gastritis (CSG), and 71/85 (83.5%) cases were chronic

atrophic

gastritis (CAG). Sixty two of the 85 (74.7%) cases with CG revealed variable degrees of activities. A hypodiploid "Sub-G1" peak was detected in 35 of 85 cases with CG. This peak was significantly higher in active chronic gastritis (ACG) than in the inactive (ICG) cases ($p < 0.005$). Proliferative activity of cases with CG was higher than in normal cases

(p

< 0.05) and in cases with ACG than in ICG ($p < 0.05$). Abnormal DNA-content (aneuploidy) was present in 16 (18.8%) of the 85 cases with CG. The presence of gastric epithelial cells with morphological changes typical of apoptosis in cases showing hypodiploid "Sub-G1" peak, high proliferation, and DNA-aneuploidy, suggests that these cells may be apoptotic bodies. Mild degree of apoptosis was present in some cases (57%) with histologically normal mucosa, while dense apoptotic bodies occurred in 87% of cases with chronic gastritis. These apoptotic bodies were constantly expressing CK1, except those in normal mucosa, suggesting that CK1 can be used as a **marker** for dying epithelial cells by **apoptosis**. CK1 was detected in 16 (100%) aneuploid cases which also showed apoptosis. CONCLUSION: The presence of apoptotic bodies in cases with chronic gastritis especially in those showing DNA-aneuploidy, may accounts for the deletion of cells with altered DNA.

L18 ANSWER 33 OF 59 MEDLINE

ACCESSION NUMBER: 96314452 MEDLINE

DOCUMENT NUMBER: 96314452 PubMed ID: 8712730

TITLE: Apoptosis in human breast and gastrointestinal **carcinomas**. Detection in histological sections with monoclonal **antibody** to single-stranded DNA.

AUTHOR: Frankfurt O S; Robb J A; Sugarbaker E V; Villa L

CORPORATE SOURCE: Department of Pathology, Cedars Medical Center, Miami, Florida 33136, USA.

CONTRACT NUMBER: CA-50677 (NCI)

SOURCE: ANTICANCER RESEARCH, (1996 Jul-Aug) 16 (4A) 1979-88.

Journal code: 8102988. ISSN: 0250-7005.

PUB. COUNTRY: Greece

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199609

ENTRY DATE: Entered STN: 19960919

Last Updated on STN: 19970203

Entered Medline: 19960910

AB We report application of a novel immunohistochemical procedure for the staining of apoptotic (AP) cells in paraffin sections using monoclonal **antibody** (MAb) to single-stranded DNA. MAb differentiated between apoptosis and necrosis and in contrast to in situ end labelling specifically stained only AP cells. AP **carcinoma** cells stained with the **antibody** were detected in 32 of 58 infiltrating human breast **carcinomas** and in 9 of 15 colon **adenocarcinomas**. Stromal cells stained with the MAb were observed in all **carcinomas**, including those in which no AP **carcinoma** cells were detected. There was a strong positive correlation between the presence of AP cells, loss of hormone receptors and a high proliferation rate in breast **carcinomas**. AP cells were present in 80-87% of receptor-negative **carcinomas**, while most of receptor-positive breast **carcinomas** did not contain AP cells. Apoptosis in **tumor** cells was detected significantly more frequently among breast **carcinomas** with high, than among **carcinomas** with low S-phase fraction. AP cells were present in 93-95% of breast **carcinomas** which were receptor-negative and had a high S-phase fraction. Immunostaining demonstrated a strong positive correlation between the loss of bcl-2 protein and intensive apoptosis in breast **carcinomas**. Association between **apoptosis** and **markers** of poor prognosis in breast **cancer** (loss of hormone receptors, intensive proliferation, loss of bcl-2 protein) indicates that apoptotic cell death is typical of more aggressive **carcinomas**.

L18 ANSWER 37 OF 59 MEDLINE

ACCESSION NUMBER: 95138702 MEDLINE

DOCUMENT NUMBER: 95138702 PubMed ID: 7836923

TITLE: Transfection of the c-myc oncogene into normal
Epstein-Barr

virus-harboring B cells results in new phenotypic and
functional features resembling those of Burkitt
lymphoma cells and normal centroblasts.

AUTHOR: Cutrona G; Ulivi M; Fais F; Roncella S; Ferrarini M

CORPORATE SOURCE: Istituto Nazionale per la Ricerca sul Cancro, IST, Genoa,
Italy.

SOURCE: JOURNAL OF EXPERIMENTAL MEDICINE, (1995 Feb 1)
181 (2) 699-711.

Journal code: 2985109R. ISSN: 0022-1007.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199502

ENTRY DATE: Entered STN: 19950314

Last Updated on STN: 20021218

Entered Medline: 19950224

AB Activated c-myc gene was introduced into the cells of three normal
Epstein-Barr virus (EBV)-positive lymphoblastoid B cell lines (LCL). The
cells were monitored for the appearance of new phenotypic and functional
features compared with the control LCL cells transfected with plasmid

that

did not contain the c-myc gene. The LCL-expressing c-myc constitutively
did not arrest growth in low serum concentration. However, the cell
number in the cultures failed to increase because of substantial cell
death. Death was due to apoptosis as demonstrated by flow cytometric
analysis of propidium iodide-stained cells, by typical DNA laddering in
gel electrophoresis, and by the inspection of Giemsa-stained cell smears.
Apoptosis was also induced by exposing the transfected cells to
antibodies directed to the immunoglobulin mu chain (a-mu-ab),
irrespective of the serum concentration in the culture. Exposure of the
cells to CD40 ligand (CD40L) or CD40 monoclonal **antibody**
prevented cell apoptosis. Upon transfection with c-myc, the LCL cells
acquired a vacuolated morphology that was never observed in control

cells.

Moreover, the expression of CD10 and CD38 was upregulated, while that of
CD39 and especially CD23 was downregulated. Unlike that observed in
certain Burkitt **lymphoma** (BL) cell lines that share the same
surface phenotype (CD10+CD38+CD23-CD39-), the c-myc-transfected cells
expressed lymphocyte function-associated (LFA) 1, LFA-3, and

intercellular

adhesion molecule 1 and grew in large clumps rather than single-cell
layers. Expression of CD10 and CD38 was particularly evident on the

cells

undergoing apoptosis, thus suggesting a correlation between the presence
of these **markers** and the **apoptotic** process. Cells
placed in conditions favoring in vitro apoptosis displayed downregulation
of Bcl-2 protein. Bcl-2 expression was, however, upregulated when the
cells were exposed to CD40L. These data indicate that the B cells
expressing c-myc constitutively acquire some of the features of normal
centroblasts and of BL cells, including the expression of CD10 and CD38,
and the propensity to undergo apoptosis, which can be prevented by

exposure to CD40L. Therefore, these cells can serve as a model system to study both BL lymphomagenesis as well as the process of B cell selection occurring in the germinal centers.

L18 ANSWER 38 OF 59 MEDLINE

ACCESSION NUMBER: 94003658 MEDLINE
DOCUMENT NUMBER: 94003658 PubMed ID: 8104556
TITLE: Le(y) antigen expression is correlated with apoptosis
(programmed cell death).
AUTHOR: Hiraishi K; Suzuki K; Hakomori S; Adachi M
CORPORATE SOURCE: Japan Immunoresearch Laboratory Co., Ltd, Gunma
Prefecture.
SOURCE: GLYCOBIOLOGY, (1993 Aug) 3 (4) 381-90.
Journal code: 9104124. ISSN: 0959-6658.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199311
ENTRY DATE: Entered STN: 19940117
Last Updated on STN: 19970203
Entered Medline: 19931118

AB Apoptosis (programmed cell death) is a basic physiological process which determines specific patterns of tissue size and shape, and balance of cell

number, during morphogenesis, and seems to play an integral role in oncogenic progression. Since dramatic changes of cellular glycosylation pattern are well known to be closely correlated with differentiation, development and oncogenesis, it is likely that similar specific changes are associated with apoptosis. However, this possibility has not been systematically investigated. We therefore carried out histological studies of many **tumours** and normal tissues for which a high incidence of apoptosis is believed to occur. Sections were stained with monoclonal **antibodies** (MoAbs) directed to carbohydrate antigens Le(y) and Le(x), proliferating cellular nuclear antigen (PCNA) and Fas (previously claimed to be an apoptosis-inducing antigen).

Antibody staining patterns were compared with morphological cell characteristics as revealed by haematoxylin/eosin staining, and DNA fragmentation patterns (a **marker** of **apoptosis**) as revealed by 3'-OH nick-end labelling technique. We found that expression of Le(y) (defined by MoAb BM1) is closely correlated with the process of apoptosis, but not with cell proliferation or necrosis. Within Le(y)-positive areas of tissue sections, typical apoptotic morphological changes and DNA fragmentation (as revealed by positive nick-end labelling)

were frequently observed in certain loci, although not all Le(y)-positive cells showed such signs of apoptosis. Le(y)-positive areas showed consistent negative staining by MoAb directed to PCNA and negative or

weak staining by MoAb directed to Fas antigen, regardless of tissue source.

No such trends were observed for Le(x) glycosylation. We conclude that Le(y)

expression is a useful phenotypic **marker** predictive of **apoptosis**, i.e. some (although not all) Le(y)-positive cells subsequently become apoptotic.

L18 ANSWER 25 OF 59 MEDLINE

ACCESSION NUMBER: 1998126040 MEDLINE

DOCUMENT NUMBER: 98126040 PubMed ID: 9466564

TITLE: **Antibody** to caspase-cleaved actin detects apoptosis in differentiated neuroblastoma and plaque-associated neurons and microglia in Alzheimer's disease.

COMMENT: Comment in: Am J Pathol. 1998 Feb;152(2):329-32

AUTHOR: Yang F; Sun X; Beech W; Teter B; Wu S; Sigel J; Vinters H V; Frautschy S A; Cole G M

CORPORATE SOURCE: Department of Medicine and Neurology, UCLA, Los Angeles, California, USA.

CONTRACT NUMBER: AG10123 (NIA)

AG10685 (NIA)

AG11125 (NIA)

+

SOURCE: AMERICAN JOURNAL OF PATHOLOGY, (1998 Feb) 152 (2) 379-89.

Journal code: 0370502. ISSN: 0002-9440.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals

ENTRY MONTH: 199803

ENTRY DATE: Entered STN: 19980319

Last Updated on STN: 20000303

Entered Medline: 19980306

AB During apoptosis, activation of a family of cysteine proteases related to interleukin-1beta-converting enzyme (ICE)-related proteases or "caspases" results in endoproteolytic cleavage of multiple substrates at specific aspartate residues. We have sought to develop new **antibody** probes for the neopeptides in protein fragments produced by ICE-related proteolytic cleavage as specific **markers** of events tightly linked to **apoptotic** mechanisms. Here, we demonstrate that an **antibody** probe specific for the C terminus of a 32-kd actin fragment produced by ICE-like activity specifically labels apoptotic but not necrotic, differentiated human neuroblastoma cells in culture.

Unlike

probes for nonspecific DNA strand breaks confined to the nucleus or cell body, this method allows the detection of cytoskeletal fragments in cell processes as well as the perikaryon long before DNA fragmentation and cell

death and therefore serves as a novel **marker** of

apoptosis-related events in distal parts of cells such as axons and dendrites. To illustrate this new tool, we show that the **antibody** detects the processes and cell bodies of degenerating neurons and plaque-associated microglia in Alzheimer's disease. In situ detection of caspase-cleaved actin provides a new means to evaluate the role of caspase activation in pathological and physiological processes.

L22 ANSWER 12 OF 18

MEDLINE

DUPLICATE 10

ACCESSION NUMBER: 97162258 MEDLINE
DOCUMENT NUMBER: 97162258 PubMed ID: 9009245
TITLE: Measurement of **apoptosis**, proliferation and three cytokines in 46 patients with myelodysplastic syndromes.
COMMENT: Comment in: Leuk Res. 1996 Nov-Dec;20(11-12):881-90
AUTHOR: Shetty V; Mundle S; Alvi S; Showel M; Broady-Robinson L; Dar S; Borok R; Showel J; Gregory S; Rifkin S; Gezer S; Parcharidou A; Venugopal P; Shah R; Hernandez B; Klein M; Alston D; Robin E; Dominguez C; Raza A
CORPORATE SOURCE: Rush Cancer Institute and the Department of Pathology, Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois 60612, USA.
SOURCE: LEUKEMIA RESEARCH, (1996 Nov-Dec) 20 (11-12) 891-900.
Journal code: 7706787. ISSN: 0145-2126.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199702
ENTRY DATE: Entered STN: 19970306
Last Updated on STN: 19980206
Entered Medline: 19970224

AB Extensive **apoptosis** or programmed cell death (PCD) of both hematopoietic (erythroid, myeloid, megakaryocytic) and stromal cells in myelodysplastic syndromes (MDS) cancels the high birth-rate resulting in ineffective hematopoiesis and has been demonstrated as the probable basis for peripheral cytopenias in MDS by our group. It is proposed that factors present in the microenvironment are inducing **apoptosis** in all the cells whether stromal or parenchymal. To investigate this hypothesis further, bone marrow biopsies from 46 MDS patients and eight normal individuals were examined for the presence of three cytokines, tumor necrosis factor-alpha (TNF-alpha), **transforming growth factor-beta** (TGF-beta) and granulocyte macrophage-colony stimulating factor (GM-CSF) and one cellular component, macrophages, by the use of monoclonal **antibodies immunohistochemically**. Results showed the presence of TNF-alpha and **TGF-beta** in 41/46 and 40/46 cases of MDS respectively, while only 15 cases showed the presence of GM-CSF. Further a significant direct relationship was found between the degree of TNF-alpha and the incidence of PCD ($p=0.0015$). Patients who showed high PCD also had an elevated TNF-alpha level. Thus, the expression of high amounts of TNF-alpha and **TGF-beta** and low amounts of the viability factor GM-CSF may be responsible for the high incidence of PCD leading to ineffective hematopoiesis in MDS.

Future

studies will be directed at attempting to reverse the lesion in MDS by using anti-TNF-alpha drugs such as pentoxifylline.

L22 ANSWER 13 OF 18

MEDLINE

DUPLICATE 11

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TITLE: Inhibition of growth and induction of **TGF-beta 1** in human hepatocellular carcinoma with androgen receptor by cyproterone acetate in male nude

mice.

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AB BACKGROUND/AIMS: Hepatocellular carcinoma possesses androgen receptor but its true role is not known. This study aimed to investigate the effect of

an anti-androgen cyproterone acetate on the growth of androgen receptor-positive hepatocellular carcinoma. METHODS: Androgen receptor-positive human hepatocellular carcinoma cells (KYN-1/SM-10) were subcutaneously transplanted into male nude mice. When the tumor size was about 10 mm, animals were subcutaneously administered cyproterone acetate (0.1 mg/day and 0.8 mg/day) or solvent alone for 21 days. Animals were serially sacrificed for measurements of testicular weight, tumor size,

and

cytosolic and nuclear androgen receptor levels in tumor. Proliferating cell nuclear antigen, transforming growth factor-alpha, and **transforming growth factor-beta 1** in tumor were investigated **immunohistochemically**, using monoclonal **antibodies**. Apoptotic activity was also studied by the in situ DNA nick end labeling method. RESULTS: Cyproterone acetate depressed testicular weight, suppressed tumor growth, and decreased both cytosolic-androgen receptor and nuclear-androgen receptor levels dose-dependently. Numbers of proliferating cell nuclear antigen-positive cells were decreased transiently with the low dose but continuously with the high dose of cyproterone acetate. Transforming growth factor-alpha expression was not influenced by cyproterone acetate, but the high dose

of

cyproterone acetate induced higher expression of **transforming growth factor-beta 1**, associated with increased numbers of apoptotic tumor cells, peaking on day 3. CONCLUSIONS: The inhibition of growth of androgen receptor-positive hepatocellular carcinoma with cyproterone acetate in male nude mice could be due to G1-phase cell cycle arrest, and to some extent **apoptosis** induced by increased synthesis of **transforming growth factor-beta 1** in tumor, caused by the direct action of cyproterone acetate through androgen receptors, as well as decreased testosterone levels in blood due to cyproterone acetate-induced

testicular

atrophy.